

**REMARKS**

The Office Action dated March 19, 2004, has been received and reviewed.

Claims 1-27 are currently pending and under consideration in the above-referenced application, each standing rejected.

Reconsideration of the above-referenced application is respectfully requested.

**Rejections Under 35 U.S.C. § 102**

Each of claims 1-9, 11-13, 15, and 21 stands rejected under 35 U.S.C. § 102(b).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single reference which qualifies as prior art under 35 U.S.C. § 102. *Verdegaal Brothers v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Lee

Claims 1-9, 13, 15, and 21 have been rejected under 35 U.S.C. § 102(b) for reciting subject matter which is allegedly anticipated by the subject matter described in K. B. LEE et al., "A New approach to Assay Endo-Type Carbohydrases: Bifluorescent-Labeled Substrates for Glycoamidases and Ceramide Glycanases," *Analytical Biochemistry*, 01 September 1995, Vol. 230, No. 1, Pages 31-36 (hereinafter "Lee").

The description of Lee is directed to a method for assaying for certain enzymes. The method of Lee includes severing a covalent link between a pair of fluorophores. Lee, Abstract. The fluorescent qualities of the fluorophore pair differ, depending upon whether the covalent link between the fluorophore pair is intact or has been severed. Lee, Abstract. Changes in fluorescence of the fluorophore pair are due to the amount of fluorescence resonance energy transfer (FRET) between the naphthyl group of one fluorophore and the dansyl group of another fluorophore. Lee, Abstract; page 31, second column, to page 32, first column. When the covalent link between the two fluorophores is severed, the energy transfer between the naphthyl group and the dansyl group no longer occurs. As a result, fluorescence from the naphthyl group

no longer quenched to the same degree, and fluorescence of the dansyl group is diminished. Lee, Abstract.

Independent claim 1 recites a biomolecular substrate that includes, among other things, core molecular backbone, a first fluorescent dye, and a second fluorescent dye. The second fluorescent dye associates with the first fluorescent dye when the biomolecular substrate is not covalently modified to form an intramolecular dye dimer. One or both of the fluorescent dyes is quenched, at least in part, by a non-fluorescence resonance energy transfer mechanism when the first and second dyes are associated with one another in the intramolecular dye dimer, as indicated by the amendment to independent claim 1. Once the biomolecular substrate is covalently modified, the dyes dissociate from one another.

It is respectfully submitted that independent claim 1 is allowable because the description of Lee is limited to FRET-fluorescence quenching. Lee includes no express or inherent description that any non-FRET-quenching occurs when the two dyes described therein are covalently separated from one another.

Therefore, Lee does not anticipate each and every element of amended independent claim 1, as would be required to maintain the 35 U.S.C. § 102(b) rejection thereof.

Claims 2-9 and 13 are each allowable, among other reasons, for depending directly from claim 1, which is allowable.

Independent claim 15 recites a method of assaying covalent biomolecular modification. The method of independent claim 15 includes providing a sample including, among other things, first and second fluorescent dyes. Prior to covalent modification of a biomolecular substrate of which the first and second fluorescent dyes are a part, the dyes form an intramolecular dimer in which quenching, including non-FRET-quenching, occurs. When the biomolecular substrate is covalently modified, the dyes dissociate.

Lee lacks any express or inherent description of an assay method that includes use of dyes that form an intramolecular dimer in which non-FRET-quenching occurs. Rather, the description of Lee is limited to FRET-quenching between two dyes of a biomolecule prior to severing the biomolecule.

Therefore, under 35 U.S.C. § 102(b), amended independent claim 15 recites subject matter which is allowable over the subject matter described in Lee.

Claim 21 is allowable, among other reasons, for depending directly from claim 15, which is allowable.

Zhang

Claims 1, 3, 5, 13, 15, and 21 are rejected under 35 U.S.C. § 102(b) for being directed to subject matter which is purportedly anticipated by the disclosure of Z. ZHANG et al., “Amylase Substrate Based on Fluorescence Energy Transfer,” Analytical Chimica Acta, 17 September 1990, Vol. 236, No. 2, Pages 251-256 (hereinafter “Zhang”).

Like Lee, the description of Zhang with respect to associations between fluorescent dyes on the same molecule is limited to FRET-quenching.

By way of contrast, when the fluorescent dyes recited in amended independent claims 1 and 15 are associated with one another in such a way as to form intramolecular dimers, non-FRET-quenching of fluorescence occurs. Therefore, Zhang does not expressly or inherently describe, or anticipate, each and every element of amended independent claim 1 or amended independent claim 15.

As such, amended independent claims 1 and 15 are directed to subject matter which, under 35 U.S.C. § 102(b), is allowable over the subject matter disclosed in Zhang.

Each of claims 3, 5, and 13 is allowable, among other reasons, for depending directly from claim 1, which is allowable.

Claim 21 is allowable, among other reasons, for depending directly from claim 15, which is allowable.

Meldal

Claims 1-5, 7-9, 13, 15, and 21 stand rejected under 35 U.S.C. § 102(b) for being drawn to subject matter which is assertedly anticipated by the subject matter disclosed in M. MELDAL et al., “Anthranilamide and Nitrotyrosine as a Donor-Acceptor Pair in Internally Quenched Fluorescent Substrates for Endopeptidases: Multicolumn Peptide Synthesis of Enzyme

Substrates for Subtilisin Carlsberg and Pepsin,” Analytical Biochemistry, 1991, Vol. 195, Pages 141-147 (hereinafter “Meldal”).

Like Lee and Zhang, Meldal also lacks any express or inherent description that quenching between two fluorescent dyes may be caused by anything other than FRET. Accordingly, it is respectfully submitted that, under 35 U.S.C. § 102(b), amended independent claims 1 and 15 are both drawn to subject matter which is allowable over that disclosed in Meldal.

Claims 2-5, 7-9, and 13 are each allowable, among other reasons, for depending directly from claim 1, which is allowable.

Claim 21 is allowable, among other reasons, for depending directly from claim 15, which is allowable.

Taliani

Claims 1, 3, 5, 7, 13, 15, and 21 are rejected under 35 U.S.C. § 102(b) for being directed to subject matter which is allegedly anticipated by the disclosure of M. TALIANI et al., “A Continuous Assay of Hepatitis C Virus Protease Based on Resonance Energy Transfer Depsipeptide Substrates,” Analytical Biochemistry 1996, Vol. 240, Pages 60-67 (hereinafter “Taliani”).

Taliani also lacks any express or inherent description that quenching of the fluorescence of one of two fluorescent dyes may be caused by anything other than FRET. It is, therefore, respectfully submitted that Taliani does not expressly or inherently describe, or anticipate, each and every element of amended independent claim 1 or amended independent claim 15, as would be required to maintain the 35 U.S.C. § 102(b) rejections thereof.

Each of claims 3, 5, 7, and 13 is allowable, among other reasons, for depending directly from claim 1, which is allowable.

Claim 21 is allowable, among other reasons, for depending directly from claim 15, which is allowable.

Zandonella

Claims 1, 3-5, 7, 12, 13, 15, and 21 stand rejected under 35 U.S.C. § 102(b) for reciting subject matter which is assertedly anticipated by the subject matter described in C. ZANDONELLA et al., “Fluorogenic Alkyl diacyl Glycerols as Substrates for the Determination of Lipase Activity and Stereoselectivity,” Journal of Fluorescence, 1997, Vol. 7, No. 1 (Supplement), Pages 185S-186S (hereinafter “Zandonella”)

The description of Zandonella, with respect to fluorescence quenching, is also limited to FRET-quenching. As Zandonella does not expressly or inherently describe that two fluorescent dyes that may be associated with one another as an intramolecular dye dimer, the fluorescence of which is at least partially quenched by a non-FRET mechanism, it is respectfully submitted that amended independent claims 1 and 15 are directed to subject matter which, under 35 U.S.C. § 102(b), is allowable over the subject matter described in Zandonella.

Claims 3-5, 7, 12, and 13 are each allowable, among other reasons, for depending directly from claim 1, which is allowable.

Claim 21 is allowable, among other reasons, for depending directly from claim 15, which is allowable.

Hirano

Claims 1-7, 9, 11, 13, 15, and 21 have been rejected under 35 U.S.C. § 102(b) for being drawn to subject matter which is purportedly anticipated by the disclosure of Japanese patent publication JP 11-56398 of Hirano et al. (hereinafter “Hirano”).

The description of Hirano is also limited to FRET-quenching between fluorescent dyes. Thus, Hirano does not expressly or inherently describe that non-FRET-quenching may occur in an intramolecular dimer including two fluorescent dyes, as would be required to maintain the 35 U.S.C. § 102(b) rejections of both amended independent claim 1 and amended independent claim 15.

Each of claims 2-7, 9, 11, and 13 is allowable, among other reasons, for depending either directly or indirectly from claim 1, which is allowable.

Claim 21 is allowable, among other reasons, for depending directly from claim 15, which is allowable.

In view of the foregoing, it is respectfully requested that the 35 U.S.C. § 102(b) rejections of claims 1-9, 11-13, 15, and 21 be withdrawn.

**Rejections Under 35 U.S.C. § 103(a)**

Claims 1-27 have been rejected under 35 U.S.C. § 103(a) for reciting subject matter which is allegedly not patentable over teachings from L. J. MACALA et al., "Measurement of cAMP-Dependent Protein Kinase Activity Using a Fluorescent-Labeled Kemptide," *Kidney International* 1998, Vol. 54, Pages 1746-1750 (hereinafter "Macala"), U.S. Patent 5,580,747 to Schultz et al. (hereinafter "Schultz"), or C. VENTURA et al., "Phorbol Ester Regulation of Opioid Peptide Gene Expression in Myocardial Cells," *The Journal of Biological Chemistry*, 15 December 1995, Vol. 270, No. 50, Pages 30115-30120 (hereinafter "Ventura"), in view of the teachings of D K. BLUMENTHAL, "Development and Characterization of Fluorescently-Labeled Myosin Light Chain Kinase Calmodulin-Binding Domain Peptides" *Molecular and Cellular Biochemistry*, 1993, Vol. 127/128, Pages 45-50 (hereinafter "Blumenthal"), U.S. Patent 5,654,419 to Mathies et al. (hereinafter "Mathies"), Hirano, Lee, Meldal, Taliani, Zandonella, and Zhang.

The standard for establishing and maintaining a rejection under 35 U.S.C. § 103(a) is set forth in M.P.E.P. § 706.02(j), which provides:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

It is respectfully submitted that a *prima facie* case of obviousness has not been established against any of claims 1-27. In particular, it is respectfully submitted that none of Macala, Schultz, Ventura, Blumenthal, Mathies, Hirano, Lee, Meldal, Taliani, Zandonella, or Zhang teaches or suggests each and every element of any of claims 1-27.

With respect to amended independent claims 1, 15, 23, 25, and 27, it is respectfully submitted that none of the references, taken individually or collectively, teaches or suggests a biomolecular substrate that includes first and second fluorescent dyes that form a quenched intramolecular dimer, the quenching of which is effected, at least in part, by a non-FRET mechanism. Rather, as noted at pages 6 and 7 of the outstanding Office Action, Macala, Schultz, and Ventura merely teach the attachment of a single dye to a molecule. Additionally, none of Blumenthal, Mathies, Hirano, Lee, Meldal, Taliani, Zandonella, or Zhang teaches or suggests that anything other than non-FRET-quenching may occur.

Likewise, none of these references teaches or suggests a kit that includes substrates that are double-labeled with fluorescent dyes that, when the substrates are not covalently modified, form an intramolecular dye dimer in which fluorescence of the dyes is quenched, at least in part, by a ground state quenching mechanism, as is recited in amended independent claim 26.

Therefore, no combination of teachings from Macala, Schultz, Ventura, Blumenthal, Mathies, Hirano, Lee, Meldal, Taliani, Zandonella, or Zhang renders the subject matter recited in any of amended independent claims 1, 15, 23, 25, 26, or 27 obvious under 35 U.S.C. § 103(a).

Claims 2-14 are each allowable, among other reasons, for depending from claim 1, which is allowable, while claims 16-22 are each allowable, among other reasons, for depending from claim 15, which is allowable, and claim 24 is allowable, among other reasons, for depending from claim 23, which is allowable.

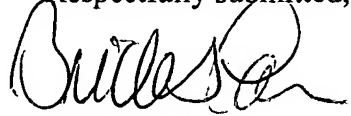
Withdrawal of the 35 U.S.C. § 103(a) rejections of claims 1-27 is, accordingly, respectfully requested.

### CONCLUSION

It is respectfully submitted that each of claims 1-27 is allowable. An early notice of the allowability of each of these claims is respectfully solicited, as is an indication that the

above-referenced application has been passed for issuance. If any issues preventing allowance of the above-referenced application remain which might be resolved by way of a telephone conference, the Office is kindly invited to contact the undersigned attorney.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Brick G. Power", written over a horizontal line.

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